

Remarks

Reconsideration of this Application is respectfully requested.

Upon entry of the foregoing amendment, claims 1-3, 5-7, and 14-25 are pending in the application, with 1, 7, 16 and 21 being the independent claims. Claims 1, 7, 16 and 21 have been amended to more particularly point out and claim the invention. These changes are believed to introduce no new matter, and their entry is respectfully requested.

Based on the above amendment and the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

Rejection under 35 U.S.C. § 102 (b)

The Examiner has rejected claims 1-3, 5-7 and 13-25 under 35 U.S.C. §102(b) as allegedly being anticipated by Iwasaki, Y., et al., *Jpn. J. Cancer Chemother.* 25:1412-1415 (1998) [hereinafter "Iwaski et al. (1998)"]; Carter, R., et al., *Br. J. Cancer* 65:37-39 (1992) [hereinafter "Carter et al."]; Ohigashi, H., et al., *Hepato-Gastroenterology* 43:338-345 (1996) [hereinafter "Ohigashi et al."]; Kitamura, M., et al., *Jpn. J. Cancer Chemother.* 17:1657-1660 (1990) [hereinafter "Kitamura et al."]; Tsuji, Y., et al., *Jpn. J. Cancer Chemother.* 23:1617-1620 (1996) [hereinafter "Tsuji et al."]; Yamaue, H., et al., *Arch. Jpn. Chir.* 59:302-309 (1990) [hereinafter "Yamaue et al."]; Iwasaki, Y., et al., *Jpn. J. Cancer Chemother.* 11:1674-1678 (1995) [hereinafter "Iwaski et al. (1995)"]; or Takahashi, N., et al., *J. Of Japan Surgical Society* 92:775-784 (1991) [hereinafter "Takahashi et al."].

Applicants respectfully traverse this rejection, reiterate and incorporate by reference the arguments made in the Reply previously filed October 18, 2002.

The claimed invention is directed, *inter alia*, to the use of angiotensin-II without an additional chemotherapeutic agent 1) to treat or prevent metastasis in cancer (e.g. claim 1) or 2) to induce the expression of β_1 integrin molecules in cancer cells (e.g. claim 7). There is clearly support in the specification for embodiments of the present invention encompassing the use of angiotensin *without* an additional chemotherapeutic agent. For example, the specification recites:

It has now been surprisingly discovered that angiotensin induces integrin production in cancer cells in contrast to its previously supposed role and that as a result angiotensin can inhibit cancer cell invasiveness.

(page 5, lines 1-3.) The specification also recites:

The present invention therefore offers a significant advance in the treatment of cancer which should permit the early and effective treatment of aggressive malignant tumours in preventing or inhibiting the spread from the primary tumour location. Angiotensin is a naturally occurring biologically active molecule which should be tolerated well by the body in contrast to existing chemotherapeutic agent or radiotherapy currently used to treat cancer.

(page 5, lines 12-22, emphasis added.) One skilled in the art would most likely recognize that the addition of chemotherapeutic agents to angiotensin would materially affect a composition of angiotensin without such agents.

The specification also provides working examples demonstrating the effect of angiotensin without an additional chemotherapeutic agent on the expression of β_1 integrin expression in a cancer cell line and on growth-factor stimulated cancer cell invasiveness.

The specification also states:

The effect of Angiotensin-II on β_1 integrin expression in MCF-7 subtype cancer cell line was studied using immunocytochemistry and the results are shown in Figure 1. The evident increase in staining of cells treated with angiotensin-II (A-II) at 10^{-5} M demonstrates the increased expression of β_1 integrin protein.

* * *

Cell surface proteins were labelled with I^{125} to study expression of the β_1 integrin subtype. After labeling, the β_1 integrin was immunoprecipitated with an anti- β_1 integrin antibody. Figure 2 shows the result of an autoradiograph demonstrating the increased expression of β_1 integrin after treatment with angiotensin-II (A-II) compared to a control sample.

* * *

The effect of angiotensin-II (A-II) in inhibiting growth factor induced stimulated cancer cell invasiveness was studied as a model system and the results are shown in Figure 3. The study was carried out using an invasion chamber in which two compartments are separated by a perforated membrane coated in matrix protein. A chemoattractant, IGF-I, was added to the medium on one side of the chamber, and the breast cancer cells to the other. Invasiveness was measured by counting the cells that migrated from one chamber to the other. Treating the cells with angiotensin-II (A-II) prior to the invasion assay led to a tenfold reduction in mean invasion from 1.58% to 0.1% ($p = 0.0011$). The invasiveness potential of the cancer cells was therefore markedly inhibited by angiotensin-II.

* * *

It was observed by light microscopy that breast cancer cells grown in culture in the presence of angiotensin-II, tended to produce larger clusters of cells than cells grown in control cultures. At the same time, angiotensin-II did not stimulate cell growth suggesting that it had a role in cell-cell adhesion[sic] and cell migration.

(page 23, line 11 through page 24, line 14.) Finally, the original claims as filed state

4. The use of an angiotensin in the preparation of a medicament for the prevention or treatment of metastasis of cancer cells.

8. The use of an angiotensin in the preparation of a medicament for the induction of expression of β_1 integrin molecules in cancer cells.

(page 25, lines 13-14 and lines 26-27.) Thus it is clear that embodiments of the invention were considered to be angiotensin without additional chemotherapeutic agents.

This is in contrast to the cited art that discusses the co-administration of angiotensin with anti-neoplastic drugs where, as indicated by the authors, angiotensin was most likely used to increase blood flow to the tumor thus aiding passage of the anti-neoplastic agent to the tumor (*See, for example Iwaski et al. (1995), English translation, page 7, lines 13-16; Takahashi et al., English translation, page 19, lines 18-21; Tsuji et al., English translation, page 4, lines 4-11.*) Nothing in the cited art suggests either 1) the use of angiotensin without an additional chemotherapeutic agent or 2) even the use of angiotensin in combination with other drugs to treat or prevent *metastasis* of cancer cells. It is new and surprising that angiotensin-II *on its own*, without an additional chemotherapeutic agent, has an effect on metastasis. Additionally, the Examiner has failed to demonstrate any mention whatsoever of the use of angiotensin to induce β_1 integrin expression in the art.

In the cited documents, the co-administration of the anti-neoplastic agent with angiotensin is directed to anti-neoplastic therapy, *i.e.* killing the cancerous cells of the tumor by the anti-neoplastic agent (*e.g.* methotrexate 5-FU, MMC, ACNU, CDNP etc.), *not* for the prevention of metastasis. Angiotensin is most likely used in the cited documents to increase the blood flow of the anti-neoplastic agent to the tumor. This is in complete contrast to the present invention which inhibits the *metastasis* of cancer cells by using only angiotensin-II.

This property of angiotensin-II is neither disclosed nor suggested in the prior art documents.

The ability of angiotensin-II to inhibit the metastasis of cancer cells is completely unexpected.

While the Examiner has rejected claims 7 and 15-25 for the same reason as above, nowhere has it been shown that the art teaches angiotensin inducing the expression of β_1 integrin. This must be shown in the art if the Examiner continues to reject the claims.

The Examiner argues that the term "consisting essentially of" should be construed as equivalent to "comprising." Applicants respectfully disagree.

Applicants direct the Examiner's attention to *PPG Industries Inc. v. Guardian Industries Corp.*, which states:

"Consisting essentially of" is a transition phrase commonly used to signal a partially open claim in a patent. Typically, "consisting essentially of" precedes a list of ingredients in a composition claim or a series of steps in a process claim. By using the term "consisting essentially of," the drafter signals that the invention necessarily includes the listed ingredients [or presumably steps] and is open to the unlisted ingredients [or steps] that do not materially affect the basic and novel properties of the invention. A "consisting essentially of" claim occupies a middle ground between closed claims that are written in a "consisting of" format and fully open claims that are drafted in a "comprising" format. See *Ex parte Davis*, 80 USPQ 448, 449-450 (Pat. Off. Bd. App. 1948); *Manual of Patent Examining Procedure* § 2111.03 (6th ed. 1997).

(48 USPQ2d 1351,1353-1354.) Applicants have provided claims that represent the "middle ground" referred to in *PPG*.

Solely in an attempt to expedite prosecution and without acquiescing in the propriety of the rejection, claims 1 and 7 have been amended to recite "a method...consisting essentially of administering to a patient in need of treatment an effective amount of a

composition consisting essentially of an angiotensin." (emphasis added.) This amendment does not preclude the addition of other steps to the method that do not materially affect the novel and basic properties of the invention. In addition, this amendment does not preclude the addition of other ingredients to the composition that do not materially affect the basic and novel properties of the invention such as, for example, excipients (See Specification, pages 8-11).

This amendment renders moot the Examiner's rejection. Therefore, the claims are not anticipated by Iwaski *et al.* (1995), Iwaski *et al.* (1998), Carter *et al.*, Ohigashi *et al.*, Kitamura *et al.*, Tsuji *et al.*, Yamaue *et al.* and Takahashi *et al.*. Accordingly, reconsideration and withdrawal of the rejection is respectfully requested.

Rejections under 35 U.S.C. § 103

The Examiner has rejected claims 1-3, 5-7 and 13-25 under 35 U.S.C. §103(a) as allegedly being obvious over Iwaski *et al.* (1998), Carter *et al.*, Ohigashi *et al.*, Kitamura *et al.*, Tsuji *et al.*, Iwaski *et al.* (1995), or Takahashi *et al.* in view of Yamaue *et al.*. Applicants respectfully traverse the rejection.

The cited documents neither disclose nor suggest the use of angiotensin without an additional chemotherapeutic agent to treat cancer, to prevent metastasis or to induce the expression of β_1 integrin. In the cited documents, the known effect of angiotensin on blood flow is utilized to control the blood flow to the tumor and the drug it is given in combination with is used to diminish the tumor size. In these documents, angiotensin is used in combination with other drugs as an adjuvant to chemotherapy. In contrast, the specification clearly describes the use of angiotensin without an additional chemotherapeutic agent to

inhibit the invasiveness of cancer cells. The examples in the specification demonstrate the utility of angiotensin in the absence of other therapeutically active ingredients, for example, by way of *in vitro* invasiveness assays (See Example 3: Effect of Angiotensin-II on breast cell cancer invasion, pages 23-24). The cited documents do not show that angiotensin without an additional chemotherapeutic agent may be used in the treatment or prevention of metastasis, as disclosed in the present invention.

The Examiner argues that the term "consisting essentially of" should be construed as equivalent to "comprising." Applicants respectfully disagree. Applicants once again direct the Examiner's attention to *PPG*, which states:

"Consisting essentially of" is a transition phrase commonly used to signal a partially open claim in a patent. Typically, "consisting essentially of" precedes a list of ingredients in a composition claim or a series of steps in a process claim. By using the term "consisting essentially of," the drafter signals that the invention necessarily includes the listed ingredients [or presumably steps] and is open to the unlisted ingredients [or steps] that do not materially affect the basic and novel properties of the invention. A "consisting essentially of" claim occupies a middle ground between closed claims that are written in a "consisting of" format and fully open claims that are drafted in a "comprising" format. See *Ex parte Davis*, 80 USPQ 448, 449-450 (Pat. Off. Bd. App. 1948); *Manual of Patent Examining Procedure* § 2111.03 (6th ed. 1997).

(48 USPQ2d 1351,1353-1354.) Applicants have provided claims that represent the "middle ground" referred to in *PPG*.

Solely in an attempt to expedite prosecution and without acquiescing in the propriety of the rejection, claims 1 and 7 have been amended to recite "a method...consisting essentially of administering to a patient in need of treatment an effective amount of a composition consisting essentially of an angiotensin." (emphasis added.) This amendment

does not preclude the addition of other steps to the method that do not materially affect the novel and basic properties of the invention. In addition, this amendment does not preclude the addition of other ingredients to the composition that do not materially affect the basic and novel properties of the invention such as, for example, excipients (*See Specification*, pages 8-11).

The Examiner asserts that

Since Yamaue teaches that lung cancer is treated by angiotensin, then it clearly would have been within the purview of the skilled artisan to treat someone suffering from lung cancer with angiotensin.

(Paper No. 17, page 4.)

Solely in an attempt to expedite prosecution, and without acquiescing in the propriety of the rejection, claims 16 and 21 have been amended to recite "a method...wherein said cancer cells are derived from at least one of the group consisting of *skin, prostate, bone and cervix.*" (emphasis added.) This amendment renders moot the Examiner's rejection. Nowhere has the Examiner cited art that suggests that angiotensin without an additional chemotherapeutic agent or with other chemotherapeutic agents may be used for the treatment or prevention of cancer derived from skin, prostate, bone or cervix. Therefore, the claims are not obvious in view of Iwaski *et al.* (1995), Iwaski *et al.* (1998), Carter *et al.*, Ohigashi *et al.*, Kitamura *et al.*, Tsuji *et al.*, Yamaue *et al.* and Takahashi *et al.*. Therefore, at a minimum, claims 16-25 are allowable. Accordingly, reconsideration and withdrawal of the rejection is respectfully requested.

Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

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Date: March 19, 2003

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Version with markings to show changes made

The claims are amended as follows:

1. (Twice Amended) A method of treatment or prevention of metastasis of cancer cells consisting essentially of administering to a patient in need of treatment a composition consisting essentially of an effective amount of an angiotensin, wherein said composition treats or prevents metastasis of cancer cells.
7. (Twice Amended) A method of inducing the expression of β_1 integrin molecules in cancer cells consisting essentially of administering to a patient a composition consisting essentially of an effective amount of an angiotensin, wherein said composition induces the expression of β_1 integrin molecules in cancer cells.
16. (Once Amended) A method of treatment or prevention of metastasis of cancer cells comprising administering to a patient in need of treatment an effective amount of an angiotensin, wherein said cancer cells are derived from at least one of the group consisting of skin, prostate, [lung,] bone and cervix, wherein said method treats or prevents metastasis of cancer cells.
21. (Once Amended) A method of inducing the expression of β_1 integrin molecules in cancer cells comprising administering to a patient an effective amount of an angiotensin, wherein said cancer cells are derived from at least one of the group

consisting of skin, prostate, [lung,] bone and cervix, wherein said method induces the
expression of β_1 integrin molecules in cancer cells.